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From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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in its capacity as elected Office

Date of mailing (day/month/year) 12 September 2000 (12.09.00)	
International application No. PCT/SI00/00002	**Applicant's or agent's file reference** 27380
International filing date (day/month/year) 17 February 2000 (17.02.00)	**Priority date** (day/month/year) 19 February 1999 (19.02.99)
Applicant FERČEJ TEMELJOTOV, Darja et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 August 2000 (16.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christelle Croci
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PATENT COOPERATION TREATY

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NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PATENTNA PISARNA, D.O.O
Copova 14
P.O. Box 1275
1001 Ljubljana
SLOVÉNIE

Date of mailing (day/month/year) 21 March 2000 (21.03.00)	
Applicant's or agent's file reference 27380	**IMPORTANT NOTIFICATION**
International application No. PCT/SI00/00002	International filing date (day/month/year) 17 February 2000 (17.02.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 February 1999 (19.02.99)
Applicant LEK, TOVARNA FARMACEVTSKIH IN KEMICNIH IZDELKOV, D.D. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

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Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 Febr 1999 (19.02.99)	P-9900039	SI	08 Marc 2000 (08.03.00)

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

RECD 15 MAY 2001
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(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
27380		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SI00/00002	17/02/2000	19/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/70		
Applicant LEK, TOVARNA FARMACEVTSKIH IN KEMICNIH IZDELKOV, D.D		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/08/2000	10.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Greif, G Telephone No. +49 89 2399 8659

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SI00/00002

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-9	as originally filed

Claims, No.:

1-15	as originally filed

Drawings, sheets:

1/2-2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 3, 6-9, 12-14
	No:	Claims	1, 4, 5, 10, 11, 15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:
D1: WO 95 22319 A (ABBOT LABORATORIES) 24 August 1995 (1995-08-24)

2. Novelty
D1 discloses pharmaceutical formulations, such as a tablet containing clarithromycin, glycerol behenate and hydroxypropyl cellulose (Table 1, example 1b; p. 7, lines 5-7), that can also contain additives like disintegrating agents or fillers (p. 5, lines 11-24) and may have an enteric coating (p. 5, lines 31-35). **D1** is therefore novelty-destroying for claims 1, 4-5 and 10-11 of the present application. Since pharmaceutical formulations of claim 1 are not novel and the antibacterial activity of clarithromycin is known, claim 15 cannot be considered as novel either. The subject-matter of claims 2-3, 6-9 and 12-14 is novel over the cited prior art (Article 33(2) PCT).

3. Inventive Step
The subject-matter of claims 2-3, 6-9 and 12 cannot be considered as inventive, since the features described in these claims, such as surfactants (claims 2 and 8), buffers (claims 3 and 9), the use of HMC (claims 6-7), and the use of an acid-resistant coating (claim 12), would be regarded by the expert in the field as usual design options in the pharmaceutical field, and would be included in tablet formulations such as described in the present application without the exercise of inventive skill.
The subject-matter of claims 13 and 14 does not fulfill the requirements of the PCT with respect to inventive step (Art. 33(3) PCT), since direct compressing of powder mixtures without prior granulation is a standard technique in the field of solid pharmaceutical formulations.

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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DIRECTLY COMPRESSIBLE MATRIX FOR CONTROLLED RELEASE OF SINGLE DAILY DOSES OF CLARITHROMYCIN

(57) Abstract

The invention refers to an improved pharmaceutical formulation for controlled release of clarithromycin or its derivatives, enabled by a novel combined matrix consisting of a fatty and a hydrophilic component, whereto also a surfactant and a pH–modulator may be added when an additional influence on the release profile of the active substance is desired.

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DIRECTLY COMPRESSIBLE MATRIX FOR CONTROLLED RELEASE OF SINGLE DAILY DOSES OF CLARITHROMYCIN

Technical Field

(IPC: C 07 G 11/00, A 61 J 3/10)

The present invention belongs to the field of pharmaceutical technology and deals with the macrolide antibiotic clarithromycin and its derivatives.

In the narrow sense the present invention deals with a novel peroral pharmaceutical formulation for controlled release of clarithromycin or its derivatives, enabled by a novel combined matrix consisting of a fatty and a hydrophilic component, whereto a surfactant and a pH modulator can be added when an additional influence on the release profile of the active substance is desired.

Background of the Invention

Clarithromycin is a slightly alkaline, practically water-insoluble and acid-sensitive macrolide antibiotic. Its solubility decreases with increased temperature and increased pH. A daily dose amounting to 500 mg has to be embedded in a relatively small matrix since a tablet should not be too large to swallow, thus leaving only a relatively narrow space for optimization of biopharmaceutical and physical-technological properties of a formulation. Consequently, in the preparation of a 24-hour tablet we face the problem of a high dose of a poorly soluble active substance and at the same time the need to ensure a repeatable and pH-independent release of clarithromycin according to a specific selected optimal time schedule.

The commercially available peroral formulation of clarithromycin with extended release contains an alginate matrix, which is known for its high dependence of the release of the active substance on the pH, whose preparation technology includes, inter alia, time-consuming and expensive processes of wet granulation, drying and

sieving and which frequently also exhibits non-repeatable dissolution profiles between different series and a slowing down of the dissolution due to aging.

Thus, the present invention is based on a need to find a simple, efficient and pH-independent formulation which will repeatably release clarithromycin over 24 hours, thereby minimizing the subjective influences with each single patient. The release rate has to ensure optimal concentrations of the active substance in blood in order to achieve therapeutic effects over a longer time period.

Prior Art

Clarithromycin is a semisynthetic antibiotic formed by methylation of erythromycin on a lactone position of C6. Its synthesis was described in US patents 4,331,803 and 4,672,109. It acts on Gram-positive bacteria and is used clinically due to the wide spectrum of antimicrobial activity. On the market it is present in the form of lacquered tablets, a suspension and extended-release tablets.

Various (per)oral formulations with clarithromycin are also described in the following patent literature:

JP patent 85/163,823 describes an oral drug containing clarithromycin and citric acid increasing the absorption of the antibiotic in the digestive tract, disintegrants, carriers and lubricants.

Withdrawn EP patent application No. 277,042 describes an oral pharmaceutical formulation with improved taste, with a coating made of special polymers (especially polyvinylacetal diethylaminoacetate - AEA) soluble in gastric juice and with average particle diameters under 60 μm.

US patent 4,808,411 describes a formulation with erythromycin or its derivatives and a carbomer, optionally in the form of particles of an ionic complex, coated with a polymer, whereat the particles can be suspended in a liquid carrier.

JP patent 89/42,625 describes the preparation of film-coated microgranules of a drug with sustained action, which, in addition to clarithromycin, also contain AEA and water.

Withdrawn EP patent application No. 302,370 and WO patent application No. 90/08,537 describe improved (per)oral formulations (oily solution, suspension, emulsion) of erythromycin and its derivatives for filling into soft gelatin capsules with N-methyl-pyrrolidone.

EP patent 420,992 describes a process for producing a taste-masked oral formulation comprising spraying a suspension of a drug into a cold aqueous solution of AEA.

US patent 5,017,383 describes a method of producing a finely coated pharmaceutical formulation comprising mixing frozen particles of a liquid medium with a drug and a coating in the form of a fine powder adhering to the surface of the particles.

US patents 5,599,556 and 5,609,909 describe the taste-masking of encapsulated clarithromycin particles with prolamine coatings prior to the preparation of a suspension.

WO patent application No. 96/34,628 describes a formulation with masked taste for oral administration (especially a dry syrup), containing an unpleasantly tasting drug, a high polymer soluble in the stomach (preferably AEA or Eudragit E) and a monoglyceride having a low melting point (preferably glyceryl monostearate) in a stable β-crystal form (transfer from meta stable α-form by means of shaking at an elevated temperature) and a method for masking the taste.

WO patent application No. 97/16,174 describes a process for water-granulation of a macrolide antibiotic with a carbomer (acrylic polymer).

US patent 5,705,190 describes a solid oral pharmaceutical formulation with controlled release containing a drug poorly soluble in water, a water-soluble alginate salt, a complex salt of alginic acid with a metal cation and an organic carboxylic acid facilitating the dissolution of the drug.

US patent 5,707,646 describes a formulation for oral administration (especially dry syrup) containing an unpleasantly tasting drug, a functional polymer (preferably AEA and/or Eudragit E) in a substance having a melting point at 40-120°C, a sugar alcohol (e.g. sorbitol) and a basic oxide (preferably MgO).

WO patent application No. 98/46,239 describes a pharmaceutical formulation with extended action containing an erythromycin derivative and a hydrophilic water-soluble polymer, showing, at oral administration, an improved taste profile and fewer gastrointestinal side effects in comparison to the usual formulation, and the preparation technology comprises, inter alia, processes of wet granulation, drying, sieving and milling.

Thus, in patent and other literature from this field there can be found numerous publications describing the composition and the preparation of various formulations with clarithromycin, but no literature source has been found that would describe such a simple process for the preparation of a clarithromycin formulation with controlled release, enabling a selected and pH-independent release profile of the active substance over 24 hours.

Description of Novel Solution with Examples

The object of the invention is a novel matrix for a controlled release of clarithromycin or its derivatives, which contains a mixture of a fatty, water-insoluble component

being the main carrier of sustained release, and of a hydrophilic component that in an aqueous medium swells, gels or thickens and thereby forms a viscous layer through which the solubilized, dissolved active substance diffuses, thus influencing the structure and consistency of the whole matrix.

To this basic matrix there may be added a wetting agent, a surfactant which softens the matrix and binds together both types of components and contributes to an easier solubilization of the active substance. The result is a matrix system which by means of a mixed mechanism of tablet erosion and diffusion releases the solubilized and/or dissolved active substance through the viscous layer.

In order to additionally influence the release profile of the active substance, to the matrix there may optionally be added a pH modulator, which is an alkaline substance, e.g. a phosphate buffer, influencing the portion of the released active substance in the stomach in relation to the intestine or decreasing the influence of the current level of acidity in any particular part of the digestive tract.

Among fatty components to be used in the embodiments of the present invention, the suitable ones are triglycerides of higher saturated fatty acids such as palmitic acid, stearic acid and behenic acid, preferably glyceryl behenate, hydrogenated oils (e.g. vegetable oils or castor oil), carnauba wax and similar. The content of the fatty component of the matrix amounts to about 10-36 % of the mass of a tablet.

Glyceryl behenate is a lipid substance, most frequently used as a lubricant, with an additional favourable property that in higher concentrations it sustains the release of active substances. Chemically, it is a mixture of glyceryl esters of behenic/docozanoic acid (C_{22}) with a low content of mono-behenate and a melting point of 69-74°C.

As the hydrophilic component there are selected substances which increase the viscosity of the micro-environment, are suspendable, stabilize the current viscous layer and may also have the ability to soften the fatty components of the matrix.

Suitable substances are alkyl-substituted cellulose ethers, preferably hydroxypropyl methylcellulose (HPMC), more preferably HPMC with low viscosity, fatty alcohols (e.g. cetyl, stearyl, cetostearyl alcohols), polysaccharides (e.g. xanthan gum, guar gum, acacia), adsorbents with a large specific surface (e.g. Mg-Al-silicates) and the like. The content of the hydrophilic component of the matrix amounts to about 5-18 % of the mass of a tablet.

HPMC is a cellulose ether, usually used for increasing the viscosity of the environment, but simultaneously it also influences the release rate of active substances. Used were low-viscous types of HPMC having viscosities (nominally for a 2 % aqueous solution at 20°C) up to about 40 cP and M_n up to about 20000 (determined by the method of osmotic pressures).

It has been found that by combining glyceryl behenate and HPMC there was obtained an exceptionally effective matrix for sustaining and controlling the release of the active substance, since in contact with an aqueous medium (also in the stomach) it swells and thereby loosens the lipid (glyceryl behenate) structure and makes possible a release of clarithromycin by diffusion through the viscous layer at a simultaneous erosion of the matrix i.e the tablet. The ratio between the lipophilic and the hydrophilic components may be between 2 : 1 and 10 : 1.

Among surfactants, anionic ones e.g. sodium docusate, sodium lauryl sulfate, and non-ionic ones can be used. The content of the surfactant amounts to about 0.5-3% of the mass of a tablet.

Sodium docusate is an anionic surfactant which in the given combination contributes to a more uniform wetting of the lipid structure and thereby facilitates the hydratation and the swelling of the matrix and makes possible a repeatable diffusion of clarithromycin from the matrix.

Tablets with clarithromycin can also be lacquered, e.g. with a suspension based on a mixture of HPMC and hydroxypropyl cellulose (HPC), according to a conventional

process or the release profile of clarithromycin is modulated by the application of an acid-resistant coating such as HPMC-phthalate.

An excellent property of the formulation of the present invention in comparison to prior art is a simple preparation technology since all ingredients are, at room temperature, just homogeneously mixed together, sieved and directly compressed into tablets, therefore no water or any other solvents are necessary.

An important technological advantage of the formulation of the present invention is also the fact that there is no need for additional lubricants, since glyceryl behenate itself, as the carrier of release control, has good lubricating properties.

Dissolution rates of clarithromycin *in vitro* from two matrix samples with controlled release over 24 hours were measured at the temperature of 37°C, during the first hour at pH = 3.0 and during the subsequent 23 hours at pH 6.8. They are shown in Figs. 1 and 2.

The invention is explained but in no way limited by the following examples.

Example 1

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E50-LV P)	150 mg
	lactose	150 mg

Dissolution test:

Dissolution profile is shown in Fig. 1.

Example 2

The composition was the same as in Example 1 only that instead of 34.5 g of lactose the same quantity of Na-docusate was used.

Example 3

Composition of one tablet:	clarithromycin	500	mg
	glyceryl behenate (Compritol 888)	350	mg
	HPMC (E50-LV P)	150	mg
	lactose	131.905	mg
	NaH_2PO_4	49.538	mg
	Na_2HPO_4	2.607	mg
	Na-docusate	5.95	mg

Dissolution test:

Dissolution profile is shown in Fig. 2.

Example 4

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E15-LV P)	150 mg
	polyvinyl pyrrolidone (K 25)	60 mg
	microcrystalline cellulose	40 mg
	stearic acid	15 mg
	SiO_2 (Aerosil 200)	5 mg
	talc	5 mg
	Ca-stearate	25 mg

Example 5

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E50-LV P)	150 mg
	polyvinyl pyrrolidone (K 25)	60 mg
	microcrystalline cellulose	40 mg
	stearic acid	15 mg
	SiO_2 (Aerosil 200)	5 mg
	talc	5 mg
	Ca-stearate	25 mg

Example 6

The composition of a tablet was the same as in Examples 1-5 only that on the tablet also an acid-resistant coating with the following composition was applied:

HPMC-phthalate	28.75 mg
triethyl citrate	2.875 mg
yellow pigment (Fe-oxide)	0.822 mg
TiO_2	0.514 mg
talc	4.039 mg

Claims

1. A pharmaceutical formulation for peroral single daily application, characterized in that it contains clarithromycin or its derivatives and a mixture of a fatty and a hydrophilic component.

2. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains a surfactant.

3. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains a pH modulator.

4. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains other pharmaceutically acceptable additives.

5. A pharmaceutical formulation according to claim 1, characterized in that the fatty component is glyceryl behenate.

6. A pharmaceutical formulation according to claim 1, characterized in that the hydrophilic component is hydroxypropyl methylcellulose of low viscosity.

7. A pharmaceutical formulation according to claim 6, characterized in that hydroxypropyl methylcellulose has a viscosity of about 15 cP.

8. A pharmaceutical formulation according to claim 2, characterized in that the surfactant is sodium docusate.

9. A pharmaceutical formulation according to claim 3, characterized in that the pH modulator is a phosphate buffer.

10. A pharmaceutical formulation according to claim 1, characterized in that it is in the form of a tablet.

11. A pharmaceutical formulation according to claim 10, characterized in that the tablet is lacquered.

12. A pharmaceutical formulation according to claim 10, characterized in that on the tablet an acid-resistant coating is applied.

13. A process for the preparation of a pharmaceutical formulation according to claim 1, characterized in that is comprises homogeneous mixing, sieving and direct compressing into tablets without use of solvents.

14. A pharmaceutical formulation for peroral single daily application, characterized in that it is prepared according to the process according to claim 13.

15. A pharmaceutical formulation according to claims 1 to 12 for use in the treatment and prophylaxis of bacterial infections.

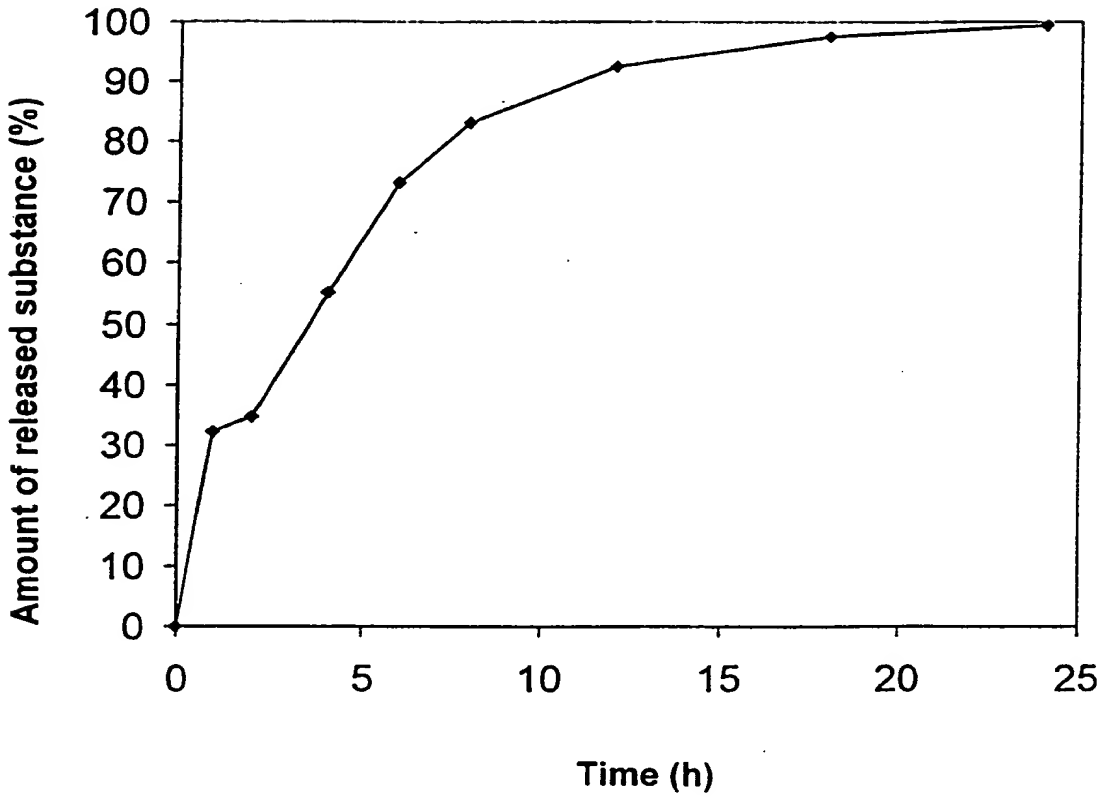
Amount of released substance (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (h)

Fig. 1

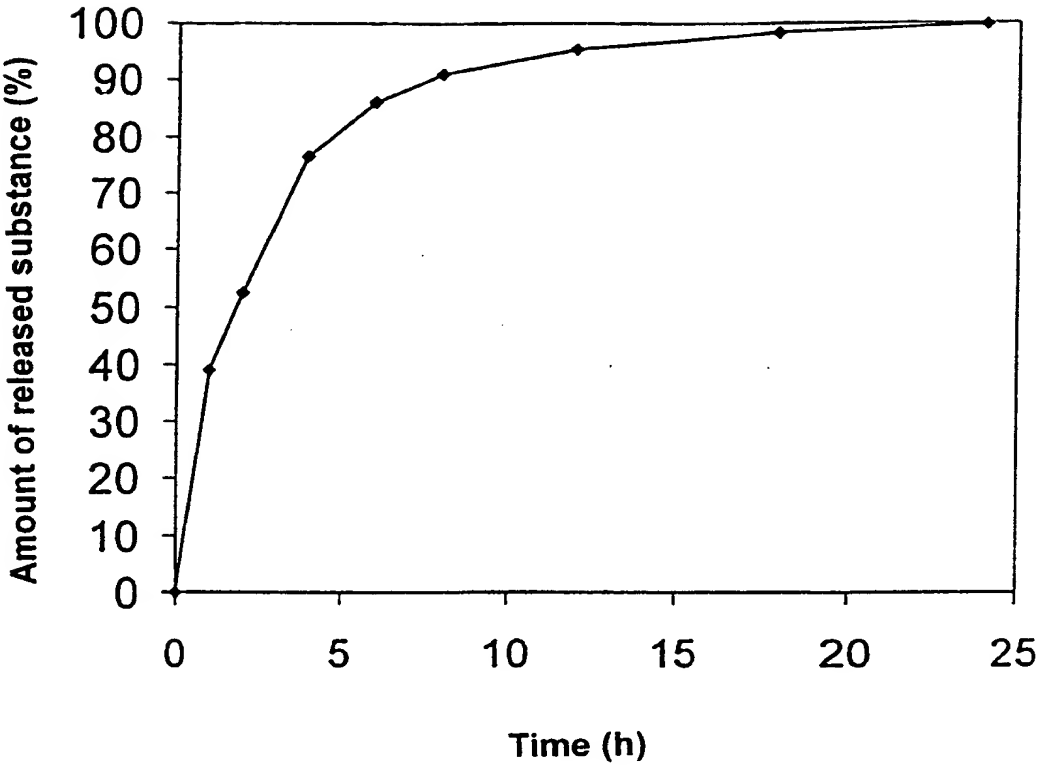
Amount of released substance (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (h)

Fig. 2

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/SI 00/00002

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70 A61K9/20 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 22319 A (ABBOT LABORATORIES) 24 August 1995 (1995-08-24) page 8; example 1B page 5, line 31 - line 35	1,4;5, 10,11, 13-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2000	11/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter: nal Application No
PCT/SI 00/00002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9522319 A	24-08-1995	EP 0744941 A	04-12-1996
		JP 9509176 T	16-09-1997
		US 6063313 A	16-05-2000

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
27380		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/SI 00/00002	17/02/2000	19/02/1999
Applicant		
LEK, TOVARNA FARMACEVTSKIH IN KEMICNIH IZDELKOV, D		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/SI 00/00002

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family member

International Application No
PCT/SI 00/00002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 9509176 T	16-09-1997
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